

REMARKS

The Office Action consisted of one rejection of the claims under 35 USC §102 and one rejection of the claims under 35 USC §103. Each of these rejections will be responded to below.

a. Response to §102 Rejections

Claims 1-4, 6-11, 14-19 and 21-23 were rejected under 35 USC §102(b) as being anticipated by Crandall (U.S. 5,560,910).

In order to anticipate a claim, the reference must show each and every element that is contained in a claim (MPEP 2131). By the present amendment, Applicant has amended the claims to include elements that are not shown by the Crandall reference.

Specifically, Applicant has amended independent claims 1 and 10 to recite that the treatment composition set forth therein includes a macrolide antibiotic. Independent claim 18 is further limited to the use of the macrolide antibiotics selected from azithromycin, erythromycin, and roxithromycin.

Crandall does not show the use of macrolide antibiotics. The term "macrolide antibiotics" defines a group of compounds having a characteristic structure, namely a large "macrolidic" ring. As is noted in Applicant's specification, examples of macrolide antibiotics include azithromycin, erythromycin, clarithromycin and roxithromycin.

Crandall does not disclose the use of macrolide antibiotics. Crandall states only in a general sense that the composition might include "antibacterial, antifungal, antiprotozoal, or antiviral agents" (of which there are thousands, or perhaps tens of thousands), and makes no mention of macrolide antibiotics.

As stated above, Applicant's independent claims 1, 10 and 18 and their respective dependents, as amended herein, include elements that expressly require the use of macrolide antibiotics. Crandall does not show this element and therefore fails to anticipate the claims. Applicant therefore respectfully submits that the rejection under 35 USC §102 has been overcome by the present amendment.

b. Response to §103 Rejections

Claims 1-23 were rejected under 35 USC §103(a) over Crandall in combination with Gupta (U.S. 6,281,199) and "current knowledge in the art." Applicant respectfully traverses this rejection.

In making the rejection, the Examiner notes that Crandall does not teach the use of azithromycin, erythromycin, or roxithromycin. Gupta is cited as showing use of azithromycin to treat arteriosclerosis, and it is stated that "as it is known in the art that Chlamydia is believed to be responsible for musculoskeletal disease (instant specification Page 6), the use of azithromycin and a penetrating agent for topically treating inflammation would have been known to one of ordinary skill in the art. Motivation to use a penetrating agent with azithromycin would have arisen in order to allow a therapeutically effective amount of azithromycin to reach the Chlamydia infection, which is likely the cause of the inflammation."

Applicant respectfully disagrees. In order to establish a *prima facie* case of obviousness, there must be some suggestion or motivation in the prior art to modify the reference or combine the references, and there must be a reasonable expectation of success: the teaching or suggestion to make a claimed combination and the reasonable expectation of success must both be found in the prior art, not in the Applicant's disclosure. (MPEP 2143) However, the assertion that "Chlamydia is believed to be responsible for musculoskeletal disease" and that motivation "would have arisen in order to allow a therapeutically effective amount of azithromycin to reach the Chlamydia infection, which is likely the cause of the inflammation" is not found in the prior art, but is instead based on Applicant's own disclosure. Applicant's disclosure makes it clear that this belief is Applicant's own hypothesis, not an admission of prior art. Therefore, this information cannot be relied on to establish obviousness.

Furthermore, the cited art itself does not provide any motivation for the proposed combination. Gupta teaches the oral administration of azithromycin in an effort to eradicate Chlamydia infections within the circulatory system, i.e., the bloodstream. The reference shows no recognition of using azithromycin to alleviate inflammation within the musculoskeletal system and other soft tissues. Consequently, neither this reference nor Crandall provides any motivation for employing azithromycin (or other macrolide antibiotics) and a penetrating agent so as to reach into such tissues.

The Office Action therefore fails to establish the first leg required for a *prima facie* case of obviousness, i.e., no suggestion or motivation has been shown for making the proposed combination. The Office Action also fails to establish the second step in a *prima facie* case of obviousness, i.e., a reasonable expectation of success.

The Office Action assumes that because Crandall teaches that a proteolytic enzyme may be used with a penetrating agent and possibly some "antibacterial, antifungal, antiprotozoal, or antiviral agents", then use of azithromycin or other macrolide antibiotic in this combination would be successful. However, the references provide no support for this assumption. The proteolytic enzymes of Crandall bear no structural resemblance whatsoever to macrolide antibiotics. As can be seen in the attached illustration of capsaicin, proteolytic enzymes are comparatively simple compounds with mostly chain-like structures. By comparison, as can be seen in the attached illustrations of azithromycin, clarithromycin and erythromycin, macrolide antibiotics are complex compounds that include large macrocyclic rings and first and second ancillary ring structures. Given these structural dissimilarities, one of ordinary skill in the art would not have had a reasonable expectation of success for the use of azithromycin in the composition that is taught by Crandall. As for Crandall's reference to "antibacterial, antifungal, antiprotozoal, or antiviral agents", represents a range of substances so broad and disparate in character as to provide no teaching regarding an expectation of success for the use of macrolide antibiotics.

Accordingly, for the reasons discussed above, the cited art fails to provide any suggestion or motivation for using azithromycin or another macrolide antibiotic in the compositions of Crandall, and also fails to provide any reasonable expectation of success for such use. The Office Action therefore fails to establish a *prima facie* case of obviousness against those claims that require the use of a macrolide antibiotic. Since Applicant's amended claims all include a limitation requiring the use of a macrolide antibiotic, Applicant respectfully requests that the rejection of the claims under 35 USC §103 be reconsidered and withdrawn.

c. Other amendments

The dependency of claims 5 and 12 has been amended in view of the cancellation of claims 4 and 11 by the present amendment.

d. Conclusion

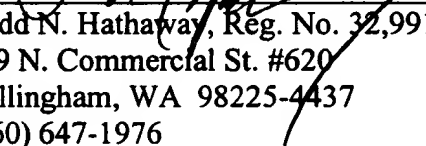
Applicant respectfully requests reconsideration of the present application in view of the amendments and remarks set forth herein. It is believed that the above-referenced claims are now in condition for allowance. If there is any matter that can be expedited by consultation with Applicant's attorney, such would be welcome. Applicant's attorney can normally be reached at the telephone number given below.

Signed at Bellingham, County of Whatcom, State of Washington this 26th day of April 2002.

Respectfully submitted,

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By


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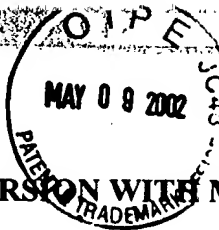
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VERSION WITH MARKINGS TO SHOW CHANGES MADE (CLAIMS)

1. (amended) A method for alleviating a disease state resulting from a microbial infection affecting sub-dermal soft tissue in a predetermined area of the body, said method comprising the steps of:

providing a treatment composition comprising, in combination:

- (iii) a selected [antimicrobial compound] macrolide antibiotic; and
- (iv) a selected mobilizing agent in an amount sufficient to enable said antimicrobial compound to penetrate into said sub-dermal soft tissue; and

applying said treatment composition to said predetermined area of the body so that said antimicrobial compound penetrates said sub-dermal soft tissue so as to reach said microbial infection therein.

5. (amended) The method of claim [4] 1, wherein the step of providing said treatment composition comprises:

selecting said antimicrobial compound from the group consisting of azithromycin, erythromycin and roxithromycin.

10. (amended) A treatment composition for alleviating a disease state resulting from a microbial infection affecting sub-dermal soft tissue in a predetermined area of the body, said treatment composition comprising:

- (iii) a selected [antimicrobial compound] macrolide antibiotic; and
- (iv) a selected mobilizing agent in an amount sufficient to enable said antimicrobial compound to penetrate into said sub-dermal soft tissue so as to reach said microbial infection therein when said composition is applied to said predetermined area of the body.

12. (amended) The treatment composition of claim [11] 10, wherein said macrolide antibiotic composition is selected from the group consisting of azithromycin, erythromycin and roxithromycin

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Intestinal amebiasis: Adults: 500 mg every 12 hours, 3-5 mg every 8 hours or 250 mg every 6 hours for 10 to 14 days. Children: 50 to 60 mg/kg/day in divided doses for 10 to 14 days. Pertussis: Although optimal dosage and duration have not been established, doses of erythromycin utilized in reported clinical studies were 40 to 50 mg/kg/day, given in divided doses for 5 to 14 days. Legionnaires' Disease: Although optimal dosage has not been established, doses utilized in reported clinical data were 1 to 4 g daily in divided doses.

HOW SUPPLIED

ERYTHROCIN STEARATE Filmtab Tablets (erythromycin stearate tablets, USP) are supplied in the following strengths and packages.

ERYTHROCIN STEARATE Filmtab, 250 mg pink tablets imprinted with the corporate logo and the Abbo-Code designation ES: (NDC 0074-6346-20)
Bottles of 100 (NDC 0074-6346-53)
Bottles of 500 (NDC 0074-6346-19)
ABBO-PAC® unit dose strip packages

of 100 tablets (NDC 0074-6346-38)
ERYTHROCIN STEARATE Filmtab, 500 mg pink tablets imprinted with the corporate logo and the Abbo-Code designation ET: (NDC 0074-6316-13)
Bottles of 100 (NDC 0074-6316-13)
Recommended Storage: Store below 86°F (30°C).

REFERENCES

1. National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*, Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25 NCCLS, Villanova, PA, December 1993.
 2. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Disk Susceptibility Tests*, Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 18, No. 24 NCCLS, Villanova, PA, December 1993.
 3. Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, the American Heart Association: Prevention of Rheumatic Fever. *Circulation*, 78(4):1082-1086, October 1988.
 4. Data on file, Abbott Laboratories, Division of Antibiotics.
- FILMTAB-Film-sealed tablets, Abbott
Ref. 03-5083-R14
Revised: November, 2000
ABBOTT LABORATORIES
NORTH CHICAGO, IL 60064, U.S.A.
PRINTED IN U.S.A.

Shown in Product Identification Guide, page 303

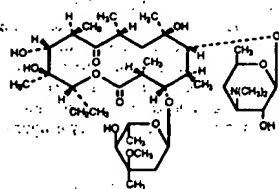
ERYTHROMYCIN

Base Filmtab®
ERYTHROMYCIN TABLETS, USP
R only

DESCRIPTION

Erythromycin Base Filmtab (erythromycin tablets, USP) is an antibacterial product containing erythromycin, USP, in a unique, nonenteric film coating for oral administration. Erythromycin Base Filmtab tablets are available in two strengths containing either 250 mg or 500 mg of erythromycin base.

Erythromycin is produced by a strain of *Saccharopolyspora erythraea* (formerly *Streptomyces erythraeus*) and belongs to the macrolide group of antibiotics. It is basic and readily forms salts with acids. Erythromycin is a white to off-white powder, slightly soluble in water, and soluble in alcohol, chloroform, and ether. Erythromycin is known chemically as (3R*, 4S*, 5S*, 6R*, 7R*, 9R*, 11R*, 12R*, 13S*, 14R*)-4-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyloxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[(3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyloxy]oxacyclotetradecane-2,10-dione. The molecular formula is C₄₇H₇₇NO₁₃, and the molecular weight is 733.94. The structural formula is:



biochemical processes in the microorganism. Erythromycin is absorbed in the small intestine, and its absorption is not affected by food. Erythromycin is largely bound to plasma proteins. After absorption, erythromycin diffuses readily into most body fluids. In the absence of meningeal inflammation, low concentrations are normally achieved in the spinal fluid but the passage of the drug across the blood-brain barrier increases in meningitis. Erythromycin crosses the placental barrier, but fetal plasma levels are low. The drug is excreted in human milk. Erythromycin is not removed by peritoneal dialysis or hemodialysis.

In the presence of normal hepatic function, erythromycin is concentrated in the liver and is excreted in the bile; the effect of hepatic dysfunction on biliary excretion of erythromycin is not known. After oral administration, less than 3% of the administered dose can be recovered in the active form in the urine.

Optimal blood levels are obtained when Erythromycin Base Filmtab tablets are given in the fasting state (at least 1/2 hour and preferably 2 hours before meals). Bioavailability data are available from Abbott Laboratories, Dept. 42W.

Microbiology

Erythromycin acts by inhibition of protein synthesis by binding 50 S ribosomal subunits of susceptible organisms. It does not affect nucleic acid synthesis. Antagonism has been demonstrated *in vitro* between erythromycin and clindamycin, lincomycin, and chloramphenicol.

Many strains of *Haemophilus influenzae* are resistant to erythromycin alone, but are susceptible to erythromycin and sulfonamides used concomitantly.

Staphylococci resistant to erythromycin may emerge during a course of erythromycin therapy. Erythromycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

Gram-positive organisms:

- Corynebacterium diphtheriae*
 - Corynebacterium minutissimum*
 - Listeria monocytogenes*
 - Staphylococcus aureus* (resistant organisms may emerge during treatment)
 - Streptococcus pneumoniae*
 - Streptococcus pyogenes*
- Gram-negative organisms:
- Bordetella pertussis*
 - Legionella pneumophila*
 - Neisseria gonorrhoeae*

Other microorganisms:

- Chlamydia trachomatis*
- Entamoeba histolytica*
- Mycoplasma pneumoniae*
- Treponema pallidum*
- Ureaplasma urealyticum*

The following *in vitro* data are available, but their clinical significance is unknown.

Erythromycin exhibits *in vitro* minimal inhibitory concentrations (MICs) of 0.5 µg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of erythromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Gram-positive organisms:

- Viridans group streptococci
- Gram-negative organisms:
- Moraxella catarrhalis*

Susceptibility Tests:

Dilution Techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of erythromycin powder. The MIC values should be interpreted according to the following criteria:

MIC (µg/mL)	Interpretation
≤0.5	Susceptible (S)
1-4	Intermediate (I)
≥8	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can

S. aureus ATCC 29213 0.12-0.5
E. faecalis ATCC 29212

Diffusion Techniques: *Staphylococcus aureus* ATCC 29213
Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15 µg erythromycin to test the susceptibility of microorganisms to erythromycin. Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15 µg erythromycin disk should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥23	Susceptible (S)
14-22	Intermediate (I)
≤13	Resistant (R)

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC of erythromycin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 15 µg erythromycin disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism	Zone Diameter (mm)
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S. aureus ATCC 25923 14-20
E. faecalis ATCC 29212 14-20

INDICATIONS AND USAGE

Erythromycin Base Filmtab tablets are indicated in the treatment of infections caused by susceptible strains of designated microorganisms in the diseases listed below. Upper respiratory tract infections of mild to moderate severity caused by *Streptococcus pyogenes*; *Streptococcus pneumoniae*; *Haemophilus influenzae* (when used concomitantly with adequate doses of sulfonamides, since many strains of *H. influenzae* are not susceptible to the erythromycin concentrations ordinarily achieved). (See appropriate antimicrobial labeling for prescribing information.)

Lower respiratory tract infections of mild to moderate severity caused by *Streptococcus pyogenes* or *Streptococcus pneumoniae*.

Listeriosis caused by *Listeria monocytogenes*.

Respiratory tract infections due to *Mycoplasma pneumoniae*.

Skin and skin structure infections of mild to moderate severity caused by *Streptococcus pyogenes* or *Staphylococcus aureus* (resistant staphylococci may emerge during treatment).

Pertussis (whooping cough) caused by *Bordetella pertussis*. Erythromycin is effective in eliminating the organism from the nasopharynx of infected individuals, rendering them noninfectious. Some clinical studies suggest that erythromycin may be helpful in the prophylaxis of pertussis in exposed susceptible individuals.

Diphtheria: Infections due to *Corynebacterium diphtheriae* as an adjunct to antitoxin, to prevent establishment of carriers and to eradicate the organism in carriers.

Erythrasma—In the treatment of infections due to *Corynebacterium minutissimum*.

Intestinal amebiasis caused by *Entamoeba histolytica* (oral erythromycins only). Extraenteric amebiasis requires treatment with other agents.

Acute pelvic inflammatory disease caused by *Neisseria gonorrhoeae*: Erythrocine Lactobionate-I.V. (erythromycin lactobionate for injection, USP) followed by erythromycin base orally, as an alternative drug in treatment of acute pelvic inflammatory disease caused by *N. gonorrhoeae* in female patients with a history of sensitivity to penicillin. Patients should have a serologic test for syphilis before receiving erythromycin as treatment of gonorrhea and a follow-up serologic test for syphilis after 3 months.

Erythromycins are indicated for treatment of the following infections caused by *Chlamydia trachomatis*: conjunctivitis of the newborn, pneumonia of infancy, and urogenital infections during pregnancy. When tetracyclines are contraindicated or not tolerated, erythromycin is indicated for the treatment of uncomplicated urethral, endocervical, or rectal infections in adults due to *Chlamydia trachomatis*.

AKINETON should be given to a pregnant woman only if clearly needed. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when AKINETON is administered to a nursing woman. **Adverse Use:** Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Atropine-like side effects such as dry mouth; blurred vision; drowsiness; euphoria or disorientation; urinary retention; postural hypotension; constipation; agitation; disturbed behavior may be seen. There usually are no significant changes in blood pressure or heart rate in patients who have been given the parenteral form of AKINETON. Mild transient postural hypotension and bradycardia may occur. These side effects can be minimized or avoided by slow intravenous administration. No local tissue reactions have been reported following intramuscular injection. If gastric irritation occurs following oral administration, it can be avoided by administering the drug during or after meals. The central anticholinergic syndrome can occur as an adverse reaction to properly prescribed anticholinergic medication. See OVERDOSAGE section for signs and symptoms of the central anticholinergic syndrome, and for treatment.

OVERDOSAGE

Signs and Symptoms: Overdose with AKINETON produces typical central symptoms of atropine intoxication (the central anticholinergic syndrome). Correct diagnosis depends upon recognition of the peripheral signs of parasympathetic blockade including dilated and sluggish pupils; warm, dry skin; facial flushing; decreased secretions of the mouth, pharynx, nose, and bronchi; foul-smelling breath; elevated temperature, tachycardia, cardiac arrhythmias, decreased bowel sounds, and urinary retention. Neuropsychiatric signs such as delirium, disorientation, anxiety, hallucinations, illusions, confusion, incoherence, agitation, hyperactivity, ataxia, loss of memory, paranoia, combative-ness, and seizures may be present. The condition can progress to stupor, coma, paralysis, and cardiac and respiratory arrest and death.

Treatment: Treatment of acute overdose revolves around symptomatic and supportive therapy. If AKINETON was administered orally, gastric lavage or other measures to limit absorption should be instituted. A small dose of diazepam or a short acting barbiturate may be administered if CNS excitation is observed. Phenothiazines are contraindicated because the toxicity may be intensified due to their antimuscarinic action, causing coma. Respiratory support, artificial respiration or vasopressor agents may be necessary. Hypertension must be reversed, fluid volume replaced and acid-base balance maintained. Urinary catheterization may be necessary.

Proton pump inhibitors for overdose is controversial. Delirium, hallucinations, coma, and supraventricular tachycardia (not ventricular tachycardias or conduction defects) may respond. If indicated, 1 mg (half this amount for children or elderly) may be given intramuscularly or by slow intravenous infusion. If there is no response within 20 minutes, an additional 1 mg dose may be given; this may be repeated until a total of 4 mg has been administered, a reversal of the toxic effects occur or excessive cholinergic signs appear. Frequent monitoring of clinical signs should be maintained. Since physostigmine is rapidly destroyed, additional doses may be required every one or two hours to maintain control. The release intervals tend to lengthen as the anticholinergic agent is metabolized, so the patient should be carefully observed for 8 to 12 hours following the last release.

Toxicity in Animals: The LD₅₀ of biperiden in the white mouse is 645 mg/kg orally, 195 mg/kg subcutaneously, and 150 mg/kg intravenously. The acute oral toxicity (LD₅₀) in rats is 750 mg/kg. The intraperitoneal toxicity (LD₅₀) of biperiden lactate in rats was 270 mg/kg and the intravenous toxicity (LD₅₀) in dogs is 222 mg/kg. In dogs under general anesthesia, respiratory arrest occurred at 33 mg/kg (intravenous) and circulatory standstill at 45 mg/kg (intravenous). The oral LD₅₀ in dogs was 340 mg/kg. Chronic toxicity studies in both rat and dog have been reported.

DOSEAGE AND ADMINISTRATION

Drug-Induced Extrapyrimal Symptoms:

Parenteral: The average adult dose is 2 mg intramuscularly or intravenously. May be repeated every half-hour until there is resolution of symptoms, but not more than four consecutive doses should be given in a 24-hour period.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Oral: One tablet one to three times daily.

Parkinson's Disease: Oral: The usual beginning dose is one tablet three or four times daily. The dosage should be individualized with the dose titrated upward to a maximum of 6 tablets (16 mg) per 24 hours.

HOW SUPPLIED

AKINETON Tablets, 2 mg each, white, embossed on one side with a triangle, bisected on the reverse and imprinted with the number "11."

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AKINETON is a registered trademark of Knoll AD.
Manufactured by:
Knoll Laboratories
A Division of
Knoll Pharmaceutical Company
Mount Olive, New Jersey 07828
Issued: 08/00

Shown in Product Identification Guide, page 303

BIAXIN Filmtab®

(clarithromycin tablets, USP)

BIAXIN® XL Filmtab®

(clarithromycin extended-release tablets)

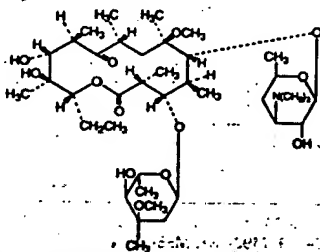
BIAXIN® Granules

(clarithromycin for oral suspension, USP)

Rx only

DESCRIPTION

Clarithromycin is a semi-synthetic macrolide antibiotic. Chemically, it is 6-O-methylerythromycin. The molecular formula is C₃₈H₆₂NO₁₃, and the molecular weight is 747.96. The structural formula is:



Clarithromycin is a white to off-white crystalline powder. It is soluble in acetone, slightly soluble in methanol, ethanol, and acetonitrile, and practically insoluble in water.

BIAXIN is available as immediate-release tablets, extended-release tablets, and granules for oral suspension. Each yellow oval film-coated immediate-release BIAXIN tablet contains 250 mg or 500 mg of clarithromycin and the following inactive ingredients:

250 mg tablets: hydroxypropyl methylcellulose, hydroxypropyl cellulose, croscarmellose sodium, D&C Yellow No. 10, FD&C Blue No. 1, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch, propylene glycol, silicon dioxide, sorbic acid, sorbitan monooleate, stearic acid, talc, titanium dioxide, and vanillin.

500 mg tablets: hydroxypropyl methylcellulose, hydroxypropyl cellulose, colloidal silicon dioxide, croscarmellose sodium, D&C Yellow No. 10, magnesium stearate, microcrystalline cellulose, povidone, propylene glycol, sorbic acid, sorbitan monooleate, titanium dioxide, and vanillin. Each yellow oval film-coated BIAXIN XL tablet contains 500 mg of clarithromycin and the following inactive ingredients: cellulose polymers, D&C Yellow No. 10, lactose monohydrate, magnesium stearate, propylene glycol, sorbic acid, sorbitan monooleate, talc, titanium dioxide, and vanillin.

After constitution, each 5 mL of BIAXIN suspension contains 125 mg or 250 mg of clarithromycin. Each bottle of BIAXIN granules contains 1250 mg (50 mL size), 2500 mg (50 and 100 mL sizes), or 5000 mg (100 mL size) of clarithromycin and the following inactive ingredients: carboxymethylcellulose, castor oil, citric acid, hypromellose phthalate, maltodextrin, potassium sorbate, povidone, silicon dioxide, sucrose, xanthan gum, titanium dioxide and fruit punch flavor.

CLINICAL PHARMACOLOGY

Pharmacokinetics:

Clarithromycin is rapidly absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability of 250-mg clarithromycin tablets was approximately 50%. For a single 500-mg dose of clarithromycin, food slightly delays the onset of clarithromycin absorption, increasing the peak time from approximately 2 to 2.5 hours. Food also increases the clarithromycin peak plasma concentration by about 24%, but does not affect the extent of clarithromycin bioavailability. Food does not affect the onset of formation of the antimicrobially active metabolite, 14-OH clarithromycin or its peak plasma concentration but does slightly decrease the extent of metabolite formation, indicated by an 11% decrease in area under the plasma concentration-time curve (AUC). Therefore, BIAXIN tablets may be given without regard to food.

In nonfasting healthy human subjects (males and females), peak plasma concentrations were attained within 2 to 3 hours after oral dosing. Steady-state peak plasma clarithromycin concentrations were attained within 3 days and were approximately 1 to 2 µg/mL with a 250-mg dose administered every 12 hours and 3 to 4 µg/mL with a 500-mg dose

administered every 8 to 12 hours. The bioavailability of clarithromycin pharmacokinetics is slight at the recommended doses of 250 mg and 500 mg administered every 8 to 12 hours. With a 250 mg every 12 hours dosing, the principal metabolite, 14-OH clarithromycin, attains a peak steady-state concentration of about 0.6 µg/mL and has an elimination half-life of 6 to 8 hours. With a 500 mg every 8 to 12 hours dosing, the peak steady-state concentration of 14-OH clarithromycin is slightly higher (up to 1 µg/mL), and its elimination half-life is about 7 to 9 hours. With any of these dosing regimens, the steady-state concentration of this metabolite is generally attained within 3 to 4 days. After a 250-mg tablet every 12 hours, approximately 20% of the dose is excreted in the urine as clarithromycin, while after a 500-mg tablet every 12 hours, the urinary excretion of clarithromycin is somewhat greater, approximately 30%. In comparison, after an oral dose of 250 mg (125 mg/5 mL) suspension every 12 hours, approximately 40% is excreted in urine as clarithromycin. The renal clearance of clarithromycin is, however, relatively independent of the dose size and approximates the normal glomerular filtration rate. The major metabolite found in urine is 14-OH clarithromycin, which accounts for an additional 10% to 15% of the dose with either a 250-mg or a 500-mg tablet administered every 12 hours.

Steady-state concentrations of clarithromycin and 14-OH clarithromycin observed following administration of 500-mg doses of clarithromycin every 12 hours to adult patients with HIV infection were similar to those observed in healthy volunteers. In adult HIV-infected patients taking 500- or 1000-mg doses of clarithromycin every 12 hours, steady-state clarithromycin C_{max} values ranged from 2 to 4 µg/mL and 5 to 10 µg/mL, respectively.

The steady-state concentrations of clarithromycin in subjects with impaired hepatic function did not differ from those in normal subjects; however, the 14-OH clarithromycin concentrations were lower in the hepatically impaired subjects. The decreased formation of 14-OH clarithromycin was at least partially offset by an increase in renal clearance of clarithromycin in the subjects with impaired hepatic function when compared to healthy subjects.

The pharmacokinetics of clarithromycin was also altered in subjects with impaired renal function. (See PRECAUTIONS AND DOSAGE AND ADMINISTRATION.)

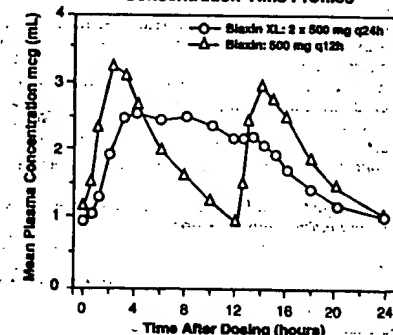
Clarithromycin and the 14-OH clarithromycin metabolite distribute readily into body tissues and fluids. There are no data available on cerebrospinal fluid penetration. Because of high intracellular concentrations, tissue concentrations are higher than serum concentrations. Examples of tissue and serum concentrations are presented below.

CONCENTRATION
(after 250 mg q12h)

Tissue Type	Tissue (µg/g)	Serum (µg/mL)
Tongue	1.6	0.8
Lung	8.8	1.7

Clarithromycin extended-release tablets provide extended absorption of clarithromycin from the gastrointestinal tract after oral administration. Relative to an equal total daily dose of immediate-release clarithromycin tablets, clarithromycin extended-release tablets provide lower and later steady-state peak plasma concentrations but equivalent 24-hour AUCs for both clarithromycin and its microbiologically-active metabolite, 14-OH clarithromycin. While the extent of formation of 14-OH clarithromycin following administration of BIAXIN XL tablets (2 × 500 mg once daily) is not affected by food, administration under fasting conditions is associated with approximately 30% lower clarithromycin AUC relative to administration with food. Therefore, BIAXIN XL tablets should be taken with food.

Steady-State Clarithromycin Plasma Concentration-Time Profiles



In healthy human subjects, steady-state peak plasma clarithromycin concentrations of approximately 2 to 3 µg/mL were achieved about 5 to 8 hours after oral administration of 2 × 500 mg BIAXIN XL tablets once daily; for

Continued on next page

top of previous page] In this study, the incidence of adverse gastrointestinal, in all patients treated with azithromycin, the common side effect was diarrhea (4%).

In comparative clinical and microbiologic studies performed in the United States, compared to an antimicrobial/beta-lactam study utilized two of the same investigators (Protocol 2 (above), and these two investigators in Efficacy Protocol 3. Efficacy Protocol 3 was not considered to be a study. Significant rates of beta-lactamase (20%) were found. Ninety-two (92) patients for clinical and microbiologic efficacy, clinical success rate (i.e., cure and improvement) with a baseline pathogen at the Day 30 for azithromycin vs. 100% for control; at the clinical success rate was 82% for 80% for control.

terminations were made at the pre-treatment visit was not reassessed at later visits. Day 30 visits, the following presumptive cure outcomes (i.e., clinical success) were observed in the following group:

(on previous page) Analysis of the above study, the incidence of primarily gastrointestinal, in all patients with azithromycin and 31% with the control. Common side effect was diarrhea/loose stools (azithromycin vs. 29% control).

In controlled studies, conducted in the azithromycin (12 mg/kg once a day for 5 days) to penicillin V (250 mg three times a day) in the treatment of pharyngitis due to documented *Streptococcus* (GABHS or *S. pyogenes*) was clinically and microbiologically superior to penicillin at Day 14 and Day 30. Clinical success (i.e., cure and improvement) efficacy rates (for the combined with documented GABHS):

(on previous page) azithromycin-susceptible *S. pyogenes* and to azithromycin following therapy. In these events, primarily gastrointestinal, were 18% on azithromycin and 13% on penicillin. Common side effects were diarrhea/loose stools (azithromycin vs. 2% penicillin), vomiting (4% penicillin), and abdominal pain (15% penicillin).

TOXICOLOGY
Intracellular phospholipid accumulation) in some tissues of mice, rats, and dogs treated with azithromycin. It has been demonstrated in various organs (e.g., eye, dorsal root ganglion, kidney, spleen, and pancreas) in azithromycin at doses which expressed orally 2 times greater than the recommended dose and in rats at doses comparable to adult human dose. This effect has been observed in azithromycin treatment. Phospholipidosis was observed to a similar extent in the tissues of dogs given daily doses of azithromycin 10 days to 80 days. Based on pharmacokinetic data, this has been seen in the rat (30 mg/kg) with a C_{max} value of 1.3 µg/mL (6 times the C_{max} of 0.216 µg/mL at the pediatric dose). Similarly, it has been shown in the dog (10 mg/kg) with a C_{max} value of 1.5 µg/mL (7 times the observed same C_{max} and drug dose in humans). On mg/m² basis, 30 mg/kg (10 mg/m²) and 10 mg/kg dose in the dog (79 mg/m²) are 0.4 and 0.6 times, respectively, the pediatric dose. This effect, similar to that seen in humans, is reversible after cessation of azithromycin. The significance of these findings for animals is unknown.

For Clinical Laboratory Standards. Antimicrobial Susceptibility Tests. 7th Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 24, NCCLS, Villanova, PA, December 1993.

For Clinical Laboratory Standards. Antimicrobial Disk Susceptibility Tests. 7th Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 24, NCCLS, Villanova, PA, December 1993.

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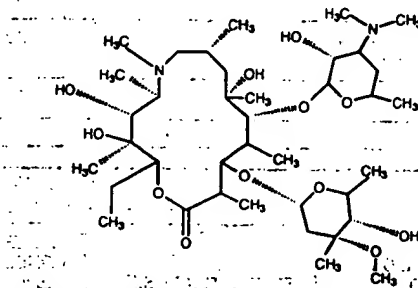
Revised January 2001

Identification Guide, page 331.

(azithromycin for oral suspension)

DESCRIPTION

ZITHROMAX® (azithromycin capsules, azithromycin tablets and azithromycin oral suspension) contain the active ingredient azithromycin, an azalide, a subclass of macrolide antibiotics, for oral administration. Azithromycin has the chemical name (2R, 3S, 4R, 5R, 6R, 10R, 11R, 12S, 13S, 14R)-13-[(2,6-dideoxy-3-C-methyl- α -L-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[(3,4,6-trideoxy-3-(dimethylamino)- β -D-xyllo-hexopyranosyl)oxy]-1-oxa-6-azacyclopentadecan-15-one. Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. Its molecular formula is $C_{38}H_{72}N_2O_{12}$, and its molecular weight is 749.0. Azithromycin has the following structural formula:



Azithromycin, as the dihydrate, is a white crystalline powder with a molecular formula of $C_{38}H_{72}N_2O_{12} \cdot 2H_2O$ and a molecular weight of 785.0.

ZITHROMAX® capsules contain azithromycin dihydrate equivalent to 250 mg of azithromycin. The capsules are supplied in red opaque hard-gelatin capsules (containing FD&C Red #40). They also contain the following inactive ingredients: anhydrous lactose, corn starch, magnesium stearate, and sodium lauryl sulfate.

ZITHROMAX® tablets contain azithromycin dihydrate equivalent to 600 mg azithromycin. The tablets are supplied as white, modified oval-shaped, film-coated tablets. They also contain the following inactive ingredients: dibasic calcium phosphate anhydrous, pregelatinized starch, sodium croscarmellose, magnesium stearate, sodium lauryl sulfate and an aqueous film, coat consisting of hydroxypropyl methyl cellulose, titanium dioxide, lactose and triacetin.

ZITHROMAX® for oral suspension is supplied in a single dose packet containing azithromycin dihydrate equivalent to 1 g azithromycin. It also contains the following inactive ingredients: colloidal silicon dioxide, sodium phosphate tribasic, anhydrous, spray dried artificial banana flavor, spray dried artificial cherry flavor, and sucrose.

CLINICAL PHARMACOLOGY

Pharmacokinetics: Following oral administration, azithromycin is rapidly absorbed and widely distributed throughout the body. Rapid distribution of azithromycin into tissues and high concentration within cells result in significantly higher azithromycin concentrations in tissues than in plasma or serum. The 1 g single dose packet is bioequivalent to four 250 mg capsules.

The pharmacokinetic parameters of azithromycin in plasma after dosing as per labeled recommendations in healthy young adults and asymptomatic HIV-seropositive adults (age 18-40 years old) are portrayed in the following chart [See first table at top of next page]

In these studies (500 mg Day 1; 250 mg Days 2-5), there was no significant difference in the disposition of azithromycin between male and female subjects. Plasma concentrations of azithromycin following single 500 mg oral and i.v. doses declined in a polyphasic pattern resulting in an average terminal half-life of 68 hours. With a regimen of 500 mg on Day 1 and 250 mg/day on Days 2-5, C_{min} and C_{max} remained essentially unchanged from Day 2 through Day 5 of therapy. However, without a loading dose, azithromycin C_{min} levels required 5 to 7 days to reach steady-state.

In asymptomatic HIV-seropositive adult subjects receiving 600-mg **ZITHROMAX®** tablets once daily for 22 days, steady state azithromycin serum levels were achieved by Day 15 of dosing.

When azithromycin capsules were administered with food, the rate of absorption (C_{max}) of azithromycin was reduced by 52% and the extent of absorption (AUC) by 43%.

When the oral suspension of azithromycin was administered with food, the C_{max} increased by 46% and the AUC by 14%.

The absolute bioavailability of two 600 mg tablets was 34% (CV=56%). Administration of two 600 mg tablets with food increased C_{max} by 31% (CV=43%) while the extent of absorption (AUC) was unchanged (mean ratio of AUCs=1.00; CV=55%).

The AUC of azithromycin in 250 mg capsules was unaffected by coadministration of an antacid containing aluminum and magnesium hydroxide with **ZITHROMAX®** (azithromycin); however, the C_{max} was reduced by 24%. Administration of cimetidine (800 mg) two hours prior to azithromycin had no effect on azithromycin absorption.

although higher peak concentrations (increased by 30 to 50%) were observed, no significant accumulation occurred. The high values in adults or apparent steady-state volume of distribution (31.1 L) and plasma clearance (630 mL/min) suggest that the prolonged half-life is due to extensive uptake and subsequent release of drug from tissues. Selected tissue (or fluid) concentration and tissue (or fluid) to plasma/serum concentration ratios are shown in the following table:

[See second table on next page]

The extensive tissue distribution was confirmed by examination of additional tissues and fluids (bone, ejaculum, prostate, ovary, uterus, salpinx, stomach, liver, and gallbladder). As there are no data from adequate and well-controlled studies of azithromycin treatment of infections in these additional body sites, the clinical significance of these tissue concentration data is unknown.

Following a regimen of 500 mg on the first day and 250 mg daily for 4 days, only very low concentrations were noted in cerebrospinal fluid (less than 0.01 µg/mL) in the presence of non-inflamed meninges.

Following oral administration of a single 1200 mg dose (two 600 mg tablets), the mean maximum concentration in peripheral leukocytes was 140 µg/mL. Concentrations remained above 32 µg/mL for approximately 60 hr. The mean half-lives for 6 males and 6 females were 34 hr and 57 hr, respectively. Leukocyte to plasma C_{max} ratios for males and females were 258 (±77%) and 175 (±60%), respectively, and the AUC ratios were 804 (±31%) and 541 (±28%), respectively. The clinical relevance of these findings is unknown. Following oral administration of multiple daily doses of 600 mg (1 tablet/day) to asymptomatic HIV-seropositive adults, mean maximum concentration in peripheral leukocytes was 252 µg/mL (±49%). Trough concentrations in peripheral leukocytes at steady-state averaged 146 µg/mL (±33%). The mean leukocyte to serum C_{max} ratio was 456 (±38%) and the mean leukocyte to serum AUC ratio was 816 (±31%). The clinical relevance of these findings is unknown.

The serum protein binding of azithromycin is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02 µg/mL to 7% at 2 µg/mL. Biliary excretion of azithromycin, predominantly as unchanged drug, is a major route of elimination. Over the course of a week, approximately 6% of the administered dose appears as unchanged drug in urine.

There are no pharmacokinetic data available from studies in hepatically or renally impaired individuals.

The effect of azithromycin on the plasma levels or pharmacokinetics of theophylline, administered in multiple doses adequate to reach therapeutic steady-state plasma levels is not known. (See PRECAUTIONS)

Mechanism of Action: Azithromycin acts by binding to the 50S ribosomal subunit of susceptible microorganisms and, thus, interfering with microbial protein synthesis. Nucleic acid synthesis is not affected.

Azithromycin concentrates in phagocytes and fibroblasts as demonstrated by *in vitro* incubation techniques. Using such methodology, the ratio of intracellular to extracellular concentration was >30 after one hour incubation. *In vivo* studies suggest that concentration in phagocytes may contribute to drug distribution to inflamed tissues.

Microbiology

Azithromycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

Aerobic Gram-Positive Microorganisms

- Staphylococcus aureus*
- Streptococcus agalactiae*
- Streptococcus pneumoniae*
- Streptococcus pyogenes*

NOTE: Azithromycin demonstrates cross-resistance with erythromycin-resistant gram-positive strains. Most strains of *Enterococcus faecalis* and methicillin-resistant staphylococci are resistant to azithromycin.

Aerobic Gram-Negative Microorganisms

- Haemophilus influenzae*
- Moraxella catarrhalis*
- "Other" Microorganisms**

- Chlamydia trachomatis*

Beta-lactamase production should have no effect on azithromycin activity.

Azithromycin has been shown to be active *in vitro* and in the prevention and treatment of disease caused by the following microorganisms:

Mycobacteria

- Mycobacterium avium* complex (MAC) consisting of:
 - Mycobacterium avium*
 - Mycobacterium intracellulare*

The following *in vitro* data are available, but their clinical significance is unknown.

Azithromycin exhibits *in vitro* minimal inhibitory concentrations (MICs) of 2.0 µg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of azithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic Gram-Positive Microorganisms

- Streptococci (Groups C, F, G)
- Viridans group streptococci

Continued on next page.

5.4 mg/kg. L. Orö, A. Wretling, *Acta Pharmacol. Toxicol.* 141 (1961).

USE: Manuf of esters for artificial fruit flavors and perfumes; as an intermediate in other chemical syntheses.

1734. n-Caproic Acid. Hexanoic acid. $C_6H_{12}O_2$; mol wt 116.16. C 62.04%, H 10.41%, O 27.55%. $CH_3(CH_2)_4COOH$. Occurs in milk fats (about 2%), in coconut oil (<1%), various palm and other oils. Prepn: Vliet *et al.*, *Org. Syn. coll.* II, 417 (1943); Reid, Ruhoff, *ibid.*, 475. Manuf by catalytic reduction of corresponding β -lactone: Caldwell, U.S. pat. 2,484,486 (1949 to Kodak); from oleic acid: Follett, Murray, U.S. pat. 2,580,417 (1952 to Arthur D. Little); from castor oil or a ricinoleate: Steadman, Peterson, U.S. pat. 2,847,432 (1958 to National Res. Corp.); by ozonolysis of tall oil unsaturated fatty acids: Maggiolo, U.S. pat. 2,865,937 (1958 to Welsbach); from 1,3-butadiene and potassium acetate in presence of $NaNH_2$: Schmerling, Toekelt, U.S. pat. 3,075,010 (1963 to Universal Oil Prod.); from cyclohexanol: Bartlett, Lippincott, U.S. pat. 3,121,728 (1964 to Esso); by catalytic oxidation of n-hexanol: Hay, U.S. pat. 3,173,933 (1965 to General Electric). Review: *Fatty Acids*, Part 1, K. S. Markley, Ed. (Interscience, New York, 2nd ed., 1960) pp 34, 37.

Oily liquid, bp 205°. Characteristic goat-like odor. mp -34°. d_4^{20} 0.9265. n_D^{20} 1.4163. Slightly soluble in water (0.082 g/100 g); readily soluble in ethanol, ether. LD_{50} orally in rats: 3.0 g/kg, H. F. Smyth, C. P. Carpenter, *J. Ind. Hyg. Toxicol.* 26, 269 (1944).

USE: Manuf of esters for artificial flavors, and of hexyl derivatives, especially hexylphenols, hexylresorcinol, etc.

1735. Caproic Aldehyde. Hexanal; caproaldehyde; hexaldehyde. $C_6H_{12}O$; mol wt 100.16. C 71.94%, H 12.08%, O 11.97%. $CH_3(CH_2)_4CHO$. Prepn: Bagard, *Bull. Soc. Chim.* 1, 307 (1907).

Liquid, d_4^{20} 0.8335. bp₁₀ 131°; bp₁₅ 28°. Autooxidizes and polymerizes, especially in the presence of traces of acid. LD_{50} orally in rats: 4.89 g/kg, Smyth *et al.*, *Arch. Ind. Hyg. Occup. Med.* 10, 61 (1954).

1736. Caprolactam. Hexahydro-2H-azepin-2-one; ϵ -caprolactam; 2-oxohexamethylenimine; 2-ketohexamethylenimine; aminocaproic lactam. $C_6H_{11}NO$; mol wt 113.16. C 63.68%, H 9.80%, N 12.39%, O 14.14%. Prepn: Wallach, *Ann.* 312, 187 (1900); 343, 43 (1905); Ruzicka *et al.*, *Helv. Chim. Acta* 4, 477 (1921); Eck, Marvel, *J. Biol. Chem.* 106, 37 (1934); Marvel, Eck, *Org. Syn. coll.* vol. II, 371 (1943); Lazier, Rigby, U.S. pat. 2,234,566 (1941 to du Pont); Chlack, U.S. pat. 2,249,177 (1941 to I. G. Farben); Ger. pat. 739,953 (1943); 745,224 (1943); P. Smith, *J. Am. Chem. Soc.* 70, 320 (1948); E. Schmitz *et al.*, *J. Prakt. Chem.* 319, 24 (1977). Purification: Kampschmidt, U.S. pat. 2,860,052 (1957 to Stamicarbon N. V.). Stabilization with aldehydes: Indest *et al.*, U.S. pat. 2,884,414 (1959 to Vereinigte Glanzstoff-Fabriken). Reviews: *CIOs Repts* no. 22 and 6, File XXXIII/Synthetic Fiber Developments in Germany, parts I & II; K. Kahr *et al.* in *Ullmann's Encyclopedia der Technischen Chemie* vol. 9, E. Bartholome *et al.*, Eds. Verlag Chemie, Weinheim, 4th ed., 1975) pp 96-114.



Hygroscopic leaflets from petr ether, mp 70°. d_4^{25} (liq) 1.02. bp₅₀ 180°; bp₁₀₀ 100°. Viscosity at 78° = 9 centipoises. Flash pt, open cup: 257°F (125°C). Freely sol in water, ethanol, ethanol, ether, tetrahydrofurfuryl alcohol, dimethylformamide. Also sol in chlorinated hydrocarbons, hexohexene, petroleum fractions. A 70% aq soln has d_4^{25} 1.01, n_D^{25} 1.4965; n_D^{20} 1.4935. LD_{50} orally in rats: 2.14 g/kg, F. Smyth *et al.*, *Am. Ind. Hyg. Assoc. J.* 30, 470 (1969). USE: Manuf of synthetic fibers of the polyamide type (Perlon) solvent for high mol wt polymers.

1737. Caproyl Chloride. Hexanoyl chloride. $C_6H_{11}ClO$; mol wt 134.61. C 53.54%, H 8.24%, Cl 26.34%, O 11.89%. $(CH_3)_4COCl$. Prepn: Brown, *J. Am. Chem. Soc.* 60,

1325 (1938). Manuf: Wygant, U.S. pat. 2,806,061 (1957 to Monsanto).

Liquid, bp 151-153°. fp -87.3°. d_4^{20} 0.9805. n_D^{20} 1.4286. Dec by water or alcohol. Sol in ether, chloroform.

1738. Caprylene. 1-Octene; octylene. C_8H_{16} ; mol wt 112.21. C 85.63%, H 14.37%. $CH_3(CH_2)_6CH=CH_2$. Prepn from appropriate alkylmagnesium bromide and allyl bromide or chloride: Geisler, Pilz, *Ber.* 95, 96 (1962); from formaldehyde or paraformaldehyde and triphenyl(phenylmethylene)phosphorane: Hauser *et al.*, *J. Org. Chem.* 28, 372 (1963); by catalytic dehydration of 2-octanol: Lundeen, Hoozer, *J. Am. Chem. Soc.* 85, 2180 (1963).

Liquid, bp 121°, bp₁₀₀ 61.5-61.7°. mp -102°. d_4^{20} 0.7149, d_4^{25} 0.7109. n_D^{20} 1.4087, n_D^{25} 1.4062. Flash pt, open cup: 70°F (21°C). Practically insol in water; misc with alcohol, ether.

1739. Caprylic Acid. Octanoic acid. $C_8H_{16}O_2$; mol wt 144.21. C 66.63%, H 11.18%, O 22.19%. $CH_3(CH_2)_6COOH$. Prepn from 1-heptene: Dupont *et al.*, *Compt. Rend.* 240, 628 (1955); by oxidation of octanol: Langenbeck, Richter, *Ber.* 89, 202 (1956). Manuf: Alexander, U.S. pat. 2,821,534 (1958 to GAF); McAlister *et al.*, U.S. pat. 3,053,869 (1962 to Standard Oil Co., Indiana). Review: *Fatty Acids*, Part 1, K. S. Markley, Ed., (Interscience, New York, 2nd ed., 1960) pp 34, 38.

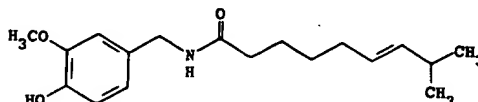
Oily liquid, bp 239.7°. Slightly unpleasant rancid taste. mp 16.7°. d_4^{20} 0.910. n_D^{20} 1.4280. Very slightly sol in water (0.068 g/100 g at 20°); freely sol in alcohol, chloroform, ether, carbon disulfide, petr ether, glacial acetic acid. LD_{50} orally in rats: 10,080 mg/kg, P. M. Jenner *et al.*, *Food Cosmet. Toxicol.* 2, 327 (1964).

USE: An intermediate in manuf of esters used in perfumery; in manuf of dyes, etc.

1740. Caprylic Aldehyde. Octanal; caprylaldehyde; octaldehyde. $C_8H_{16}O$; mol wt 128.21. C 74.94%, H 12.58%, O 12.48%. $CH_3(CH_2)_6CHO$. Prepn: Stephen, *J. Chem. Soc.* 127, 1874 (1925).

Liquid, d_4^{20} 0.821. bp₁₀₀ 163.4°; bp₂₀ 72°; bp₃₀ 60°. n_D^{20} 1.41667. Slightly sol in water; misc with alc, ether.

1741. Capsaicin. N-[(4-Hydroxy-3-methoxyphenyl)methyl]-8-methyl-6-nonenamide; trans-8-methyl-N-vanillyl-6-nonenamide; N-(4-hydroxy-3-methoxybenzyl)-8-methyl-non-trans-6-enamide. $C_{18}H_{27}NO_3$; mol wt 305.40. C 70.78%, H 8.91%, N 4.59%, O 15.72%. Pungent principle in fruit of various species of *Capsicum*, *Solanaceae*. Isolated from paprika and cayenne: Thresh, *Pharm. J. and Trans.* 7, 21 (1876); Micko, *Z. Nahr. Genussm.* 1, 818 (1898). See Beilstein 13, suppl. 1, 322. Early structure study: Nelson, *J. Am. Chem. Soc.* 42, 597 (1920). Synthesis: Späth, Darling, *Ber.* 63, 737 (1930); L. Crombie *et al.*, *J. Chem. Soc.* 1955, 1025; O. P. Vig *et al.*, *Indian J. Chem.* 17B, 558 (1979). Constitution and biosynthesis: D. J. Bennet, E. W. Kirby, *J. Chem. Soc. C* 1968, 442. Pharmacology: Molnar *et al.*, *Acta Physiol.* 35, 369 (1969). Capsaicin is a powerful irritant; administration causes intense pain in humans and exptl animals. Prolonged treatment causes insensitivity to painful stimuli; in newborn rats it induces selective degeneration of certain primary sensory neurones which mediate chemogenic pain, see G. Jancso *et al.*, *Nature* 270, 741 (1977); R. Gamse, *Arch. Pharmacol.* 320, 205 (1982); P. Holzer *et al.*, *Neurosci. Letters* 31, 253 (1982). Capsaicin pretreatment also induces long-lasting desensitization of airway mucosa to various mechanical and chemical irritants: J. M. Lundberg, A. Saria, *Nature* 302, 251 (1983). Reviews: Molnar, *Arzneimittel-Forsch.* 15, 718 (1965); Walker, Gavern, *Mfg. Chem. Aerosol News* 39 (6), 35 (1968); R. M. Virus, G. F. Gebhart, *Life Sci.* 25, 1273 (1979); Y. Monsereenusorn *et al.*, *CRC Crit. Rev. Toxicol.* 10, 321-339 (1982).



Monoclinic, rectangular plates, scales from petr ether, mp 65°. bp_{0.01} 210-220° (air-bath temp). uv max: 227, 281 nm

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